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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,795	04/20/2000	HARTMUT KUPPER	0480/001178	4157

26474 7590 03/25/2003

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EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT PAPER NUMBER

1647

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/529,795

Applicant(s)

KUPPER ET AL.

Examiner

Jegatheesan Seharaseyon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 23 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☐ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/23/03 in Paper Nos: 10 and 11 has been entered. An action on the RCE follows.
2. Claims 1-7 are pending. Therefore claims 1-7 are under consideration.
3. The text of those sections of title 35, U. S. Code not included in this action can be found in the previous office action (Paper No: 6 and 8).

#### ***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph are withdrawn***

4. Applicant's arguments have obviated the rejection of claims 1-7 under 35 USC § 112, 1<sup>st</sup> paragraph for lack of adequate written description and lack of enablement.

#### ***Claim Rejections - 35 USC § 103 (a) Rejection withdrawn***

5. The rejection of claims 1-7 under 35 USC § 103(a) as obvious over Stenzel et al. (US 6,235,281), is withdrawn in favor of new grounds of rejections.

#### ***Double Patenting Rejection withdrawn***

6. The claims 1-7 rejected under obviousness-type double patenting over Stenzel et al. (US 6,235,281), is withdrawn in favor of new grounds of rejections.
7. New grounds of rejections.

***New Claim Rejections - 35 USC § 112***

8. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 3 and 5 are rejected as being vague and indefinite in the recitation of the term "measurement period". It is unclear as to what is meant by the term "measurement period". Claims 4 and 6 are rejected insofar as they depend on rejected claims 1 and 5.

***New Claim Rejections - 35 USC § 103***

9a. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stenzel et al. (U.S. Patent No: 6,235,281) in view of Kraghsbjerg et al. (1996).

The instant invention (claims 1-4) is directed to the use of TNF antagonists which include anti-TNF antibody for the treatment of septic disorders characterized by elevated serum levels of interleukin-6 (IL-6). The invention is also directed to a kit comprising TNF antagonist in claims 5 and 6. Finally, a method for establishing whether a patient suffering from sepsis is to be treated with TNF antagonist (claim 7).

Stenzel et al. teaches a method of treating a patient with septicemia (a septic disorder) with elevated IL-6 levels (above 1000pg/ml) by administering TNF antagonist. Please note that the examiner is considering, in view of the specification, the IL-6 levels indicated in claim 1 of U.S. Patent No: 6,235,281 to be 1000pg/ml and not 1.000p/ml. The levels of IL-6 in '281, are clearly above the 500pg/ml threshold of the instant claims.

In addition, Patent '281 teaches that a distinct reduction in mortality is observed when the septicemic patients who are treated have IL-6 levels of 500 pg/ml or more at the start of the treatment meeting the limitation of claim 2 (column 2, lines 17-19). They also teach that the TNF antagonist used is a F (ab')<sub>2</sub> fragment of a monoclonal anti-TNF antibody (column 3, lines 39-40). It is routine in the management of patients with chronic conditions, to monitor proinflammatory cytokines (IL-6) as markers over a period of time to determine the change in the levels. It would also be routine to package the antagonist into a kit for the routine commercial exploitation of the invention for treating septic disorders. However, Stenzel et al. does not describe the change of IL-6 level in the serum of patients with septic disorders or measuring the change of IL-6 in a 4-10 hr window.

Kragstbjerg et al. describe the monitoring of several cytokines including IL-6 over several hours after admission with positive blood cultures and clinical signs of infection (abstract). Samples were obtained on admission, after 1, 4, 12, 18, 24h, and then daily (abstract) to measure the cytokine levels. They report that the level of IL-6, G-CSF, TNF- $\alpha$ , and IL-8 correlated with severity and high levels of IL-6 and G-CSF identified patients at risk of a fatal course.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time of the instant invention was made to modify the method of Stenzel et al. by administering TNF antagonists to patients with high level of serum IL-6, because Kragstbjerg teaches the measuring of IL-6 and patients with high levels of IL-6 are at risk of a fatal course. One of ordinary skill in the art, at the time of the instant invention

would have been motivated to use TNF antagonist to treat septicemic patients with higher levels of IL-6 to reverse the fatal course over a defined period of time. Therefore, the instant invention is prima facie obvious over Stenzel et al. (U.S. Patent No: 6,235,281) in view of Kragstbjerg et al. (1996).

8b. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stenzel et al. (WO 95/20978) in view of Kragstbjerg et al. (1996).

The instant invention (claims 1-4) is directed to the use of TNF antagonists which include anti-TNF antibody for the treatment of septic disorders characterized by elevated serum levels of interleukin-6 (IL-6). The invention is also directed to a kit comprising TNF antagonist in claims 5 and 6. Finally, a method for establishing whether a patient suffering from sepsis is to be treated with TNF antagonist (claim 7).

Stenzel et al. (WO 95/20978) teaches the use of TNF antagonists to treat diseases characterized by elevated interleukin-6 serum levels (abstract). Stenzel et al. teaches a method of treating a patient with septicemia (a septic disorder) with elevated IL-6 levels (above 1000pg/ml) by administering TNF antagonist. They also teach that the TNF antagonist used is a F(ab')<sub>2</sub> fragment of a monoclonal anti-TNF antibody (page 5, lines 1-2). The serum levels of IL-6 in WO 95/20978 document are clearly above the 500pg/ml threshold of the instant claims. In addition, WO 95/20978 document teaches that a distinct reduction in mortality is observed when the septicemic patients who are treated have IL-6 levels of 500 pg/ml or more at the start of the treatment. It is routine in the management of patients with chronic conditions, to monitor proinflammatory

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cytokines (IL-6) as markers over a period of time to determine the change in the levels. It would also be routine to package the antagonist into a kit for the routine commercial exploitation of the invention for treating septic disorders. However, Stenzel et al. does not describe the change of IL-6 level in the serum of patients with septic disorders or measuring the change of IL-6 in a 4-10 hr window.

The relevance of Kraghsbjerg et al. (1996) has been set forth above (see paragraph 8a).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time of the instant invention was made to modify the method of Stenzel et al. by administering TNF antagonists to patients with high level of serum IL-6, because Kraghsbjerg teaches the measuring of IL-6 and patients with high levels of IL-6 are at risk of a fatal course. One of ordinary skill in the art, at the time of the instant invention would have been motivated to use TNF antagonist to treat septicemic patients with higher levels of IL-6 to reverse the fatal course over a defined period of time. Therefore, the instant invention is prima facie obvious over Stenzel et al. (WO 95/20978) in view of Kraghsbjerg et al. (1996).

#### ***New Double Patenting Rejection***

9. Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. U.S. Patent No: 6,235,281 in view of Kraghsbjerg et al. (1996).

The instant invention (claims 1-4) is directed to the use of TNF antagonists which include anti-TNF antibody for the treatment of septic disorders characterized by elevated serum levels of interleukin-6 (IL-6). The invention is also directed to a kit comprising TNF antagonist in claims 5 and 6. Finally, a method for establishing whether a patient suffering from sepsis is to be treated with TNF antagonist (claim 7).

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,235,281. Although the conflicting claims are not identical, they are not patentably distinct from each other because the TNF antagonist which are monoclonal antibodies are used in both instance. The levels of IL-6 in '281, are clearly above the 500pg/ml threshold of the instant claims. In addition, Patent '281 teaches that a distinct reduction in mortality is observed when the septicemic patients who are treated have IL-6 levels of 500 pg/ml or more at the start of the treatment (column 2, lines 17-19). It is also routine in the management of patients with chronic conditions to monitor proinflammatory cytokines (IL-6) as markers over a period of time to determine the change in the levels. It would have also been obvious to package the antagonist into a kit for the routine commercial exploitation of the invention for treating septic disorders as described in claims 4 and 5 of the instant invention. Claim 7 of the instant invention is a routine mathematical description of the change overtime of the level of IL-6. However, Stenzel et al. does not describe the change of IL-6 level in the serum of patients with septic disorders or measuring the change of IL-6 in a 4-10 hr window.

The relevance of Kraghsbjerg et al. (1996) has been set forth above (see paragraph 8a).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time of the instant invention was made to modify the method of Stenzel et al. by administering TNF antagonists to patients with high level of serum IL-6, because Kraghsbjerg teaches the measuring of IL-6 and patients with high levels of IL-6 are at risk of a fatal course. One of ordinary skill in the art, at the time of the instant invention would have been motivated to use TNF antagonist to treat septicemic patients with higher levels of IL-6 to reverse the fatal course over a defined period of time. Thus, claims 1- 7 are obvious over claims 1-3 of U.S. Patent No: 6,235,281 in view of Kraghsbjerg et al. (1996).

10 No claims are allowable over prior art.

#### **Contact Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS  
March 24, 2003

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